CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-489

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA#: 74-489 **SPONSOR**: Copley
DOSAGE FORM: Hydrocortisone valerate cream
STRENGTHS(s): 0.2%.
TYPE OF STUDY: Pivotal bioequivalence study.
STUDY SITE:

STUDY SUMMARY: The sponsor submitted a pivotal bioequivalence study based on June 2, 1995, OGD guidance. Test and reference products were compared at a dose duration equal to population ED_{50} (90 minutes) for the reference product, Westcort[R] 0.2% cream (Westwood Squibb). This ED_{50} value was obtained from a pilot dose-response study previously submitted to the Division of Bioequivalence.

Comparison of test and reference products was based on the Area Under the Effect Curve (AUEC) using chromameter and visual assessment of vasoconstriction. Based on the chromameter data, 90% confidence intervals for the AUEC were within the acceptable range of Furthermore, the AUEC-90% confidence intervals based on visual scores data were also within the acceptable range of The results of the pivotal bioequivalence study demonstrate that Copley's hydrocortisone valerate 0.2% cream is bioequivalent to the reference product, Westcort[R] 0.2% cream, manufactured by Westwood Squibb.

***IN VITRO* RELEASE** DATA: The sponsor did not submit *in vitro* release data. Based on the June 2, 1995, OGD guidance, such data are not required to support *in vivo* bioequivalence of the test product..

PRIMARY REVIEWER: Gur J.P. Singh, Ph.D. **BRANCH:** II

INITIAL: /S/ DATE 5-9-97

TEAM LEADER: Shriniwas Nerurkar, Ph.D. **BRANCH:** II

INITIAL: /S/ DATE 5/20/1997

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Nicholas Fleischer, Ph.D.

INITIAL: /S/ DATE 5/29/97

DIRECTOR, OFFICE OF GENERIC DRUGS

INITIAL: DATE

ANDA 74-489

Copley Pharmaceutical, Inc.
Canton Commerce Center
Attention: W.E. Brochu, Ph.D.
25 John Road
Canton MA 02021

MAY 30 1997

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Hydrocortisone Valerate Topical Cream, 0.2%.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MAY 2 9 1997

Hydrocortisone Valerate

Topical Cream, 0.2%
ANDA #74-489
Reviewer: Gur J.P. Singh.
File #74489S.O96

Copley
25 John Road
Canton, Mass 02021
Submission Date
December 15, 1995
August 20, 1996.

Review of a pharmacodynamic bioequivalence study

BACKGROUND

This application contains two studies; a pilot dose-response study on the reference listed formulation (Westcort[R] 0.2% cream), and a pivotal bioequivalence study. These studies are based on the June 2, 1995, OGD guidance for documentation of *in vivo* bioequivalence of multisource dermatologic corticosteroids.

Both studies are based on the vasoconstrictor assay, and in these studies the dose of drug delivered is a function of the duration of exposure of skin to the formulation. The dose is therefore referred to as "dose-duration". The pilot study was conducted to determine ED_{50} for the reference listed drug (RLD). The dose-duration to be used in the bioequivalence study comparing the test and the reference product was based on the ED_{50} value obtained from the pilot dose-response study on the RLD. The pivotal bioequivalence study also employed two calibrator dose durations D_1 and D_2, in addition to the ED_{50} value, where D_1 was half of the bioequivalence dose (ED_{50}) and D_2 was 2 times of the bioequivalence dose.

Pilot study performed by was previously submitted, and that study was found to be acceptable to the Division of Bioequivalence (Review date: June 14, 1995). Based on that review, the Division of bioequivalence recommended the D1, ED_{50} and D2 dose durations of 45, 90 and 180 minutes, respectively. The sponsor has used these dose durations for the pivotal bioequivalence study. Note that the population ED_{50} of 90 minutes was determined by "Naive Pool" analysis based on the tools available to the reviewer at that time. Subsequently, however, the reviewer has analyzed the pilot study data using the population mixed affect modeling (MEM) approach. Based on the MEM analysis of chromameter data population ED_{50} was found to be 174 minutes. The Comments section of this review includes discussion on the impact, on the outcome of the bioequivalence study, of using a dose duration shorter than the population ED_{50}.

PIVOTAL BIOEQUIVALENCE STUDY

The pivotal bioequivalence study was first submitted on December 15, 1995. That study was found to be incomplete by the Division of Bioequivalence due to deficiencies listed in an abbreviated review (Review date: April 16, 1996).

On August 20, 1996, the sponsor submitted satisfactory responses to the above deficiencies listed in Agency letter of May 13, 1996. Henceforth, the review of this application is based on all data submitted hitherto.

OBJECTIVE: To study establish *in vivo* bioequivalence of Copley's hydrocortisone valerate 0.2% cream to the reference product, Westcort[R] 0.2% cream manufactured by Westwood Squibb.

STUDY SITE, PERSONNEL AND DATES: The vasoconstrictor study was performed at

Principal Investigator:
Sub-investigators:

Bio-statistician:

Dosing Dates: Group 1 (#1-20): October 10, 1995,
Group 2 (#21-40): October 28, 1995 and
Group 3 (#41-60): November 11, 1995.

STUDY PROTOCOL AND INFORMED CONSENT: The protocol used for this study (#9412304, Revision 3, September 19, 1995) and Informed Consent were approved by the (pp 44-45, vol 2.1)

SUBJECT SELECTION: Potential subjects were screened for vasoconstrictor response to the reference listed drug Westcort[R] 0.2% cream. One 10 μL application of the RLD was applied to the upper arm above the fore arm and left in place for 1 hour. The site was evaluated visually after 6-8 hours after application. All subjects were selected based on a demonstrated skin blanching response.

Sixty (60) healthy, Caucasian, female volunteers screened above were enrolled for this study. The age of these subjects was in the range of 18 - 49 years. The weight range for these volunteers was 98-165 lbs. These subjects were accepted based on acceptable medical history, negative pregnancy test and a signed informed consent. The exclusion criteria used for this study were the following:

- History of allergy to hydrocortisone, corticosteroids, creams, lotions, ointments or cosmetics.
- History or concurrent evidence of chronic infectious, cardiac, pulmonary, bronchial, hepatic or renal disease.
- Skin coloration which would interfere with assessment of skin blanching.
- Use of systemic corticosteroids within 30 days, pharmacological agents which may affect vasoconstrictor response within 28 days, prescription medicine within 7 days, over-the-counter medication with 72 hours, and alcohol and caffeine within 48 hours prior to dosing.
- Use of topical steroids on flexor surface of forearm within 30 days of dosing.
- Use of any creams, emollients or similar products on forearms within 24 hours of dosing.
- Use of tobacco products within 30 days.
- Drug or alcohol addiction requiring treatment within 12 months.
- Positive pregnancy test.

STUDY DESIGN: The pivotal study was conducted as a one-period study involving randomized applications of the test and reference products to both arms along with the replicate applications of the calibrator doses (D_1 and D_2) of the reference product and untreated control sites on each arm. The treatment randomization assured complementary applications on left and right arm as given in the following example:

ANTECUBITAL FOSSA

Right Arm		Left Arm	
Site	Treatment	Site	Treatment
8	Untreated	16	Untreated
7	D1	15	D2
6	Test	14	Ref
5	Untreated	13	Untreated
4	D2	12	D1
3	Ref	11	Test
2	Ref	10	Test
1	Test	9	Ref

Wrist

Treatment assignments shown above represent an example; randomized treatment assignments for all subjects are given on pages 38-41 (vol 2.1). The following active drug treatments were administered:

Test: Hydrocortisone valerate 0.2% cream, Copley Pharmaceuticals, Inc., Lot #679Z02, Lot size: [redacted] applied for a dose duration of 90 minutes.

Ref: Westcort[R] topical cream 0.2% (Lot #81F109, expiry date: 12/96) manufactured by Westwood Squibb Pharmaceuticals, applied for a dose duration of 90 minutes.

D_1: Westcort[R] topical cream 0.2% (Lot #81F109, expiry date: 12/96) manufactured by Westwood Squibb Pharmaceuticals, applied for a dose duration of 45 minutes.

D_2: Westcort[R] topical cream 0.2% (Lot #81F109, expiry date: 12/96) manufactured by Westwood Squibb Pharmaceuticals, applied for a dose duration of 180 minutes.

TREATMENT ADMINISTRATION: Subjects were treated in three groups of 20. The forearm of each subject was washed with mild soap and gently dried within two hours prior to dosing. Eight (8) circular application sites (approximate diameter 1.6 cm) were designated on the flexor surface of each arm. Sites were not placed within 3 cm of the wrist or antecubital fossa. Using a 250 μL Hamilton syringe, 10 μL application of active drug were applied to six (6) sites on each arm as shown in the schematics above, which based on the design recommended on the June 2, 1995 OGD guidance. The products were evenly spread within each site using the conical tip of a 1.5 mL polypropylene microcentrifuge tube. All sites were kept unoccluded throughout the study.

The application of active treatments was staggered. Treatments representing all three dose durations were removed at the same time following the "staggered application/synchronized removal" scheme recommended in the June 2, 1995 OGD guidance. However this method is not consistent with the one used for the pilot dose response study. That study was based on the "Synchronized application/staggered removal" method. The Comments section of this review includes rationale for acceptability of the different methods of drug applications used in the pilot and the pivotal studies.

HOUSING AND MEALS: All subjects checked in at least 12 hours before dosing. Meals were served at traditional times. Caffeine and alcohol were restricted. Water was provided *ad lib* throughout the study. The subjects were released on day 2, approximately 27 hours after drug application. Subjects were instructed to avoid contact with water on

their arms, extreme temperature and strenuous exercise during the study. Tight clothing on the fore arm was not permitted.

ASSESSMENT OF VASOCONSTRICTION: All sights were assessed for skin blanching under standard lighting and at room temperature prior to drug applications, and at 0, 2, 4, 6, 8, 12, 21 and 24 hours after drug removal. Vasoconstrictor response was assessed using chromameter) readings taken in duplicate. The degree of skin blanching was also assessed visually using the following scoring system:

SCORE	SKIN SURFACE CONDITION
0	No pallor; no change from surrounding.
1	Mild pallor; slight or indistinct outline of application site.
2	Moderate pallor; discernable outline of application site.
3	Intense pallor; clean, distinct outline of application site.

DATA ANALYSIS: Chromameter data for the untreated and treated sites were corrected for the baseline values. The data normalized for the baseline were further corrected for changes in the untreated skin by subtracting the average of baseline-adjusted untreated spot values from the active spot data, for a given arm. The "corrected baseline-adjusted data" obtained in this manner was used for the trapezoidal computation of the area under the effect curve (AUEC) . The AUEC was used as the pharmacodynamic metric to compare the vasoconstrictor response of test formulations.

The ratio of mean AUEC value (average of left and right arm values) for D2 and D1 was calculated for each subject. Subjects whose D2/D1 ratio was ≥ 1.25 were considered to be "evaluable detectors" and included in the statistical analyses.

The AUEC values for visual assessment of skin blanching were calculated in the manner described for the chromameter data.

The AUEC data based on visual and chromameter readings were used to calculate the 90% Confidence Intervals using Locke's method, as recommended in the OGD guidance.

RESULTS

Clinical Conduct of the Study: All sixty (60) subjects dosed in this study completed the two days of evaluation. Three adverse events were reported in this study. These were nausea (subject #22 and 36), and runny nose (subject #23). These events were not related to administration of study formulations.

Accuracy of Pharmacodynamic Metric Data: Vasoconstrictor responses of test and reference products were compared based on the chromameter assessment and visual scoring. The reviewer has verified the correction of the chromameter raw data for the baseline and changes that occurred in the untreated skin. The corrected data were used for calculation of the pharmacodynamic metric, $AUEC_{0-24}$. For the presentation of chromameter AUEC data the sponsor reversed the sign from negative to positive. The reversal of sign, in this manner, poses problems in selection of "evaluable subjects" in the manner described in the June 2, 1995 guidance. Therefore all chromameter AUEC were multiplied by "-1", and their accuracy verified. The resulting $AUEC_{0-24}$ data showed values identical to those calculated by the reviewer (see table 1, attachment). The visual-score AUEC's reported by the sponsor were also found to be accurate.

"Evaluable Subjects": Based on the OGD guidance "evaluable subjects" are those which exhibit $AUEC\text{-}D_2/AUEC\text{-}D_1$ ratio of ≥ 1.25, and this guidance recommends the inclusion of only "evaluable subjects" data in statistical analyses for documentation of bioequivalence. Based on the data submitted by the firm there were 41 evaluable subjects based chromameter assessment and 40 such subjects based on visual scoring of skin blanching (Tables 2 & 3, attachment). However, the evaluable subjects were not the same in both categories; there were some subjects which qualified for bioequivalence evaluation based on both methods of assessment, whereas the others were qualified on one or the other method.

Evaluation of Bioequivalence: $AUEC_{0-24}$ data for chromameter and visual assessment of skin blanching are given in tables 4 and 5 (attachment). The presence of both positive and negative AUEC values in the chromameter data set precludes the use of log-transformation and the standard two-sided t-test procedure for calculation of the 90% confidence intervals. Instead, the OGD guidance recommends the use of Locke's method *(J. Pharmac. Biopharm.*, 12:649-65, 1984).

The bioequivalence data based on reviewer's calculation of confidence intervals using $AUEC_{0-24}$ data for "evaluable subjects" and Locke's method are given below:

ASSESSMENT METHOD	AUEC0-24		TEST/REF	90% - CI
	TEST	REF		
Chromameter (N = 41)	-25.36 (50)	-27.91 (47)	0.91	84% - 98%
Visual (N=40)	29.02 (40)	32.95 (36)	0.88	84% - 92%

$AUEC_{0-24}$ data are given as mean (%CV).

The confidence intervals comparing the test and the reference product are with the conventional acceptable range of 80-125%. Therefore based on these results the test and reference product are bioequivalent.

Correlation between chromameter and visual assessment of vasoconstriction. OGD guidance allows assessment of bioequivalence based on visual assessment of vasoconstriction if a correlation can be established between chromameter and visual assessment. Based on the above summary of bioequivalence data, the test product is bioequivalent to the reference product based on either methods of assessment of vasoconstriction. Nonetheless, the reviewer computed correlation between $AUEC_{0-24}$ values based on chromameter and visual assessment. The results of these analyses are summarized in figure 1 (attachment). Though chromameter and visual data were showed poor correlation (r^2 = 0.296) it has no bearing on the outcome of this study, as the test product meets bioequivalence requirements based on chromameter data.

***IN VITRO* RELEASE DATA:** The sponsor did not submit *in vitro* release data. Based on the June 2, 1995 OGD Guidance, such data are not required to support bioequivalence of the test product..

PRODUCT COMPOSITION (NOT TO BE RELEASED UNDER FOI):

Compositions of Copley's hydrocortisone valerate 0.2% cream and Westcort[R] 0.2% cream (Reference product, NDA #17950). Ingredient strengths are given as percent concentrations in finished products.

Ingredient	TEST	REF
Hydrocortisone Valerate	0.21*	0.2
Petrolatum, White Stearyl Alcohol Propylene Glycol Amphoteric-9 Carbomer 940 Sodium Phosphate, Anhydrous (Dibasic) Sodium Phosphate, Dried Sodium Lauryl Sulfate Sorbic Acid Water		

Concentrations in the test product of all inactive ingredients are less than/or equal to those listed in Inactive Ingredients Guide (1996) for same route of administration.

COMMENTS

1. As mentioned in the Background section, sponsor's estimation of population ED_{50} for Westcort[R] 0.2% cream was based on "Naive pool" analysis of the dose response data, and it determined an ED_{50} of approximately 90 minutes. The reviewer also determined approximately same value of ED_{50} using the "naive pool" method. However the naive pool analysis may not provide ED_{50} representative of the population as the predicted and observed data may not be correlated. Therefore, the reviewer calculated population ED_{50} using the " mixed effect modeling" approach. Based on this method population ED_{50} value for the chromameter data was found to be 174 minutes.

Bioequivalence data used for product evaluation in the pivotal study are based on an ED_{50} of 90 minutes. Since this value is approximately half of the population ED_{50}, it is important to consider how this may affect bioequivalence evaluation. The premise of the pilot-pivotal study concept endorsed by Generic Drugs Advisory Committee was to make sure that the test and reference products are compared on the sensitive region of the dose-response curve, *i.e.*, in the region of 20% to 80% of the E_{max}, based on the E_{max} model. This range of pharmacodynamic response extrapolates (on the dose axis) to dose range from one fourth of ED_{50} to four times ED_{50}. Comparisons of products at doses $>ED_{50}$ is not recommended because pharmacodynamic responses become insensitive to doses that differ over an order of magnitude.

Research performed by the Agency has indicated that the intra-subject variability in pharmacodynamic response of dermatologic corticosteroids is greatest at doses below the ED_{50} and it decreases as the administered dose increases with respect to the ED_{50} (Singh et al,,1995, *Clinical Pharmacology and Therapeutics*. **57**:181). The same study also indicated that the width of the 90% confidence intervals was greatest at doses below the ED_{50} and it became smaller as the dose was increased. The confidence interval width became insensitive to doses > ED_{80}. These results suggest that if a sponsor used a dose duration < ED_{50}, the products are compared at much more steeper portion of the dose response curve. As a results, it may be harder for the sponsor to meet the bioequivalence intervals when the pivotal study dose < ED_{50}, than when it is equal to the ED_{50}, as the pharmacodynamic assay may probably be more sensitive to differences in drug delivery from the test and reference products at doses of smaller magnitude. Therefore a dose less than the population ED_{50} used for bioequivalence comparisons is acceptable.

2. OGD guidance emphasized consistency between the pilot and pivotal studies with regard to the method of drug application and removal. However, methods for application and removal of creams were different between these studies. The pilot study was based on synchronized application/staggered removal, and the pivotal study used staggered application/synchronized removal method.

The above difference in methods between the pilot and pivotal studies raises issue regarding the appropriateness of the dose duration (equal to the ED_{50}) used for the pivotal study. In reviewer's opinion, the dose duration used for comparison of test and reference products was appropriate because:

> Based on the population analysis of pilot study data performed by the reviewer, the ED_{50} values for the chromameter and visual data were 174 minutes (%CV, 121) and 175 minutes (%CV, 57) respectively. Furthermore the same analysis showed that, based on posterior Bayesian estimates, ED_{50} value for majority of subjects were >90 minutes . For the chromameter

data the proportion of study population with ED_{50} > 90 min was 67%. If the population ED_{50} determined from the pilot study and its distribution was approximately the same for the pivotal study population, one would expect nearly 67% of subjects to qualify as "evaluable subjects". It is interesting to note that 68% (41/60) of subjects dosed in the pivotal study qualified as "evaluable subjects", based on chromameter data.

The objective of conducting pilot dose-response study is to determine approximate population ED_{50} based on which the dose durations D_1 and D_2 are determined. The selection of evaluable subjects based on D_1 and D_2, which bracket ED_{50}, ensures that the test and reference products' responses remain on unsaturated portion of the individual dose-response curve. Therefore the dose duration used for comparison of these products should be appropriate, as long as bioequivalence is based on data of only "evaluable subjects".

3. All sixty subjects dosed for this study completed the evaluations. For bioequivalence evaluation there were 41 and 40 "evaluable subjects" based on the chromameter and visual assessment of vasoconstriction, respectively.

4. Based on the chromameter evaluation of skin blanching, test product's $AUEC_{0-24}$ was 9% lower than that of the reference product. The 90% confidence intervals comparing these products were within the acceptable limit of 80-125%.

5. The sponsor also measured vasoconstriction using the visual scores method. Based on this procedure, the confidence intervals were also within the limits of 80% - 125%.

6. Based on both chromameter and visual assessments of skin blanching, the test product is bioequivalent to the reference product.

RECOMMENDATIONS

1. The *in vivo* bioequivalence study conducted by Copley Pharmaceuticals comparing its hydrocortisone valerate 0.2% cream (lot #679Z02) to the reference product, Westcort^R 0.2% cream (lot #81F109) has been found to be acceptable to the Division of Bioequivalence. The results of this vasoconstrictor study demonstrate that Copley's hydrocortisone valerate 0.2% cream is bioequivalent to the reference product, Westcort^R 0.2% cream manufactured by Westwood Squibb Pharmaceuticals.

From the bioequivalence standpoint the sponsor has met requirements of *in vivo* bioequivalence on its hydrocortisone valerate 0.2% cream.

/S/

Gur J.P. Singh, Ph.D.
Review Branch II
Division of Bioequivalence.

/S/

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR: _____ 5/6/1997

CONCUR: /S/ DATE 5/29/97
for Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence.

Table 1: Verification of AUEC values based on chromameter data

			Hours after drug removal									AUEC (0-24)		
SUB	TRT	ARM	0	2	4	6	8	10	12	21	24	Reviewer (A)	Sponsor (B)	A/B
1	D1	LT	0									-37.67	-37.67	1.00
1	D2	LT	1									-25.45	-25.45	1.00
1	R1	LT	0									-33.61	-33.61	1.00
1	R2	LT	0									-34.32	-34.32	1.00
1	T1	LT	-1									-44.96	-44.96	1.00
1	T2	LT	1									-27.61	-27.61	1.00
1	D1	RT	-0									-41.22	-41.22	1.00
1	D2	RT	-2									-49.69	-49.69	1.00
1	R1	RT	-1									-46.46	-46.46	1.00
1	R2	RT	-1									-53.48	-53.48	1.00
1	T1	RT	-1									-53.45	-53.45	1.00
1	T2	RT	-1									-39.56	-39.56	1.00
2	D1	LT	-0									-16.48	-16.48	1.00
2	D2	LT	-0									-34.43	-34.43	1.00
2	R1	LT	-1									-46.32	-46.32	1.00
2	R2	LT	0									-6.60	-6.60	1.00
2	T1	LT	0									-11.69	-11.69	1.00
2	T2	LT	0									-0.60	-0.60	1.00
2	D1	RT	-0									-10.79	-10.79	1.00
2	D2	RT	-1									-21.54	-21.54	1.00
2	R1	RT	0									-3.99	-3.99	1.00
2	R2	RT	0									-12.76	-12.76	1.00
2	T1	RT	-0									-3.41	-3.41	1.00
2	T2	RT	0									-15.17	-15.17	1.00
3	D1	LT	1									-21.97	-21.97	1.00
3	D2	LT	0									-21.60	-21.60	1.00
3	R1	LT	1									-21.09	-21.09	1.00
3	R2	LT	0									-28.96	-28.96	1.00
3	T1	LT	-0									-53.76	-53.76	1.00
3	T2	LT	0									-27.20	-27.20	1.00
3	D1	RT	0									-45.96	-45.96	1.00
3	D2	RT	-0									-52.66	-52.66	1.00
3	R1	RT	1									-37.20	-37.20	1.00
3	R2	RT	1									-4.03	-4.03	1.00
3	T1	RT	1									-44.91	-44.91	1.00
3	T2	RT	-0									-59.81	-59.81	1.00
4	D1	LT	1									14.32	14.32	1.00
4	D2	LT	0									-6.65	-6.65	1.00
4	R1	LT	1									-0.46	-0.46	1.00
4	R2	LT	-0									-6.29	-6.29	1.00
4	T1	LT	-0									-13.26	-13.26	1.00
4	T2	LT	-0									-9.07	-9.07	1.00

Table 2: AUEC D2/AUEC-D1 ratios (ANDA #74-489) based on chromameter data

SUB	D1	D2	D2/D1	SUB	D1	D2	D2/D1
1			0.95	31			0.92
2			2.05	32			1.92
3			1.09	33			1.53
4			-8.79	34			2.27
5			1.87	35			12.01
6			1.78	36			1.62
7			1.97	37			0.88
8			1.86	38			7.42
9			1.35	39			4.57
10			1.27	40			1.72
11			1.39	41			1.89
12			-2.19	42			1.14
13			1.39	43			1.03
14			0.28	44			1.54
15			1.44	45			1.96
16			0.55	46			0.93
17			4.42	47			1.40
18			1.48	48			0.62
19			3.27	49			1.73
20			1.60	50			0.98
21			2.09	51			1.91
22			0.78	52			0.81
23			1.44	53			1.54
24			2.01	54			1.59
25			0.73	55			1.78
26			5.00	56			0.42
27			1.15	57			11.65
28			3.66	58			1.69
29			187.41	59			2.13
30			0.53	60			2.59
				Mean	-20.03	-32.07	
				SD	14.09	15.64	
				%CV	70	49	

The individual subject AUEC(0-24) data represent average value of left and right arm replicates.

Highlighted cells indicate D2/D1 >1.25

Table 3: AUEC D2/AUEC-D1 ratios (ANDA #74-489) based on visual scores data

SUB	D1	D2	D2/D1
1			0.90
2			-
3			1.06
4			3.40
5			-
6			1.50
7			1.60
8			1.75
9			0.87
10			1.25
11			1.13
12			2.76
13			1.09
14			-
15			11.93
16			3.43
17			4.81
18			-
19			1.30
20			-
21			1.61
22			0.84
23			1.53
24			1.61
25			1.30
26			1.38
27			1.91
28			1.73
29			1.33
30			1.31

SUB	D1	D2	D2/D1
31			1.15
32			1.93
33			1.25
34			-
35			1.73
36			1.71
37			1.58
38			1.72
39			2.86
40			1.98
41			1.42
42			1.02
43			1.50
44			1.20
45			1.14
46			1.03
47			2.27
48			3.63
49			1.88
50			1.17
51			1.32
52			1.75
53			1.95
54			1.86
55			2.17
56			2.18
57			2.02
58			1.12
59			1.12
60			4.87

Mea	24.40	37.98
SD	14.8	14.4
%CV	61	38

The individual subject AUEC(0-24) data represent average value of left and right arm replicates.

Highlighted cells indicate D2/D1 >1.25

Table 4. Individual subject test and reference product's AUEC(0-24) values based on chromameter data (ANDA #74-489)

All Subjects

AUEC (0-24)			
SUB	TEST	REF	TEST/REF
1			0.99
2			0.44
3			2.03
4			1.41
5			0.58
6			0.92
7			0.81
8			1.59
9			1.19
10			0.82
11			1.10
12			0.46
13			0.95
14			0.70
15			0.88
16			0.94
17			1.32
18			0.08
19			0.92
20			0.14
21			0.73
22			0.02
23			1.14
24			0.70
25			1.28
26			0.50
27			1.09
28			1.30
29			0.46
30			1.07

AUEC (0-24)			
SUB	TEST	REF	TEST/REF
31			0.83
32			1.16
33			0.85
34			1.03
35			1.35
36			1.36
37			1.10
38			0.75
39			1.08
40			1.63
41			1.14
42			0.80
43			0.99
44			1.22
45			0.68
46			0.71
47			1.04
48			0.46
49			1.19
50			1.08
51			0.87
52			0.99
53			0.67
54			0.96
55			0.57
56			0.96
57			2.35
58			0.98
59			0.64
60	-20.67		0.66
Mean	-25.08	-27.21	
SD	13.17	13.35	
%CV	53	49	
n	60		

The individual subject AUEC(0-24) data represent average value of left and right arm replicates.

Shaded cells at the left indicate test and reference product values used for bioequivalence comparisons, as these subjects showed D2/D1 >1.25

Subjects with D2/D2 >1.25

AUEC (0-24)			
SUB	TEST	REF	TEST/REF
2			0.44
5			0.58
6			0.92
7			0.81
8			1.59
9			1.19
10			0.82
11			1.10
13			0.95
15			0.88
17			1.32
18			0.08
19			0.92
20			0.14
21			0.73
23			1.14
24			0.70
26			0.50
28			1.30
29			0.46
32			1.16
33			0.85
34			1.03
35			1.35
36			1.36
38			0.75
39			1.08
40			1.63
41			1.14
44			1.22
45			0.68
47			1.04
49			1.19
51			0.87
53			0.67
54			0.96
55			0.57
57			2.35
58			0.98
59			0.64
60			0.66
Mean	-25.36	-27.91	
SD	12.61	13.17	
%CV	50	47	
n	41		

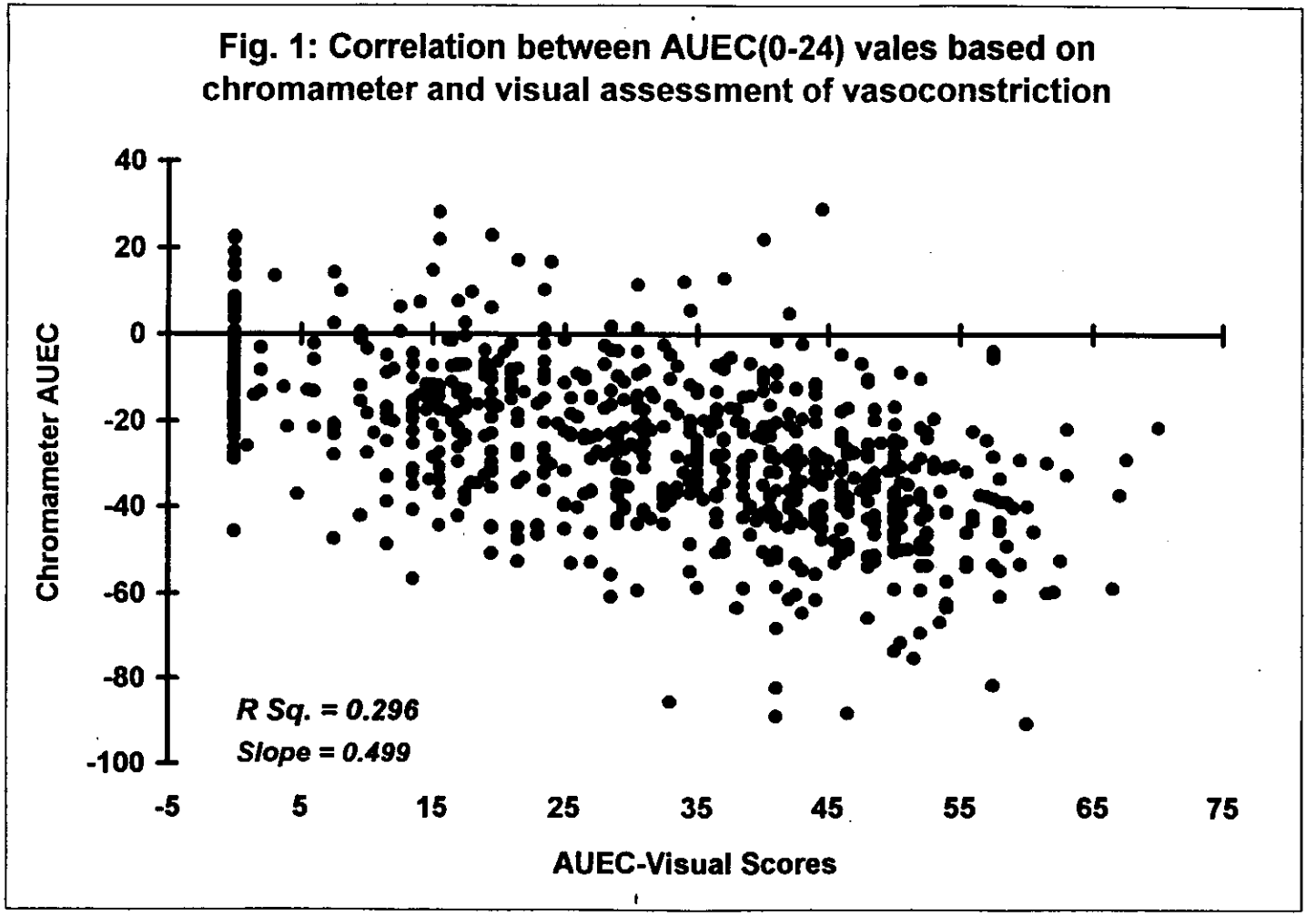
Table 5. Individual subject test and reference product's AUEC(0-24) values based on visual scores data (ANDA #74-489)

All Subjects								Subjects with D2/D2 >1.25			
AUEC (0-24)				AUEC (0-24)				AUEC (0-24)			
SUB	TEST	REF	TEST/REF	SUB	TEST	REF	TEST/REF	SUB	TEST	REF	TEST/REF
1			0.93	31			1.03	4			1.08
2			0.43	32			0.88	6			0.84
3			0.83	33			1.04	7			0.81
4			1.08	34			0.34	8			0.77
5			1.89	35			0.72	10			1.22
6			0.84	36			0.77	12			0.80
7			0.81	37			0.76	15			1.08
8			0.77	38			1.12	16			1.16
9			0.97	39			0.17	17			0.71
10			1.22	40			0.85	19			0.81
11			0.97	41			0.75	21			0.89
12			0.80	42			0.99	23			0.95
13			0.70	43			1.04	24			0.88
14			1.10	44			0.71	25			0.80
15			1.08	45			0.67	26			0.61
16			1.16	46			0.92	27			0.99
17			0.71	47			0.87	28			0.92
18			-	48			0.73	29			1.10
19			0.81	49			0.90	30			0.64
20			0.28	50			0.76	32			0.88
21			0.89	51			0.84	33			1.04
22			0.81	52			1.04	35			0.72
23			0.95	53			0.88	36			0.77
24			0.88	54			0.79	37			0.76
25			0.80	55			0.88	38			1.12
26			0.61	56			0.99	39			0.17
27			0.99	57			0.66	40			0.85
28			0.92	58			0.99	41			0.75
29			1.10	59			0.92	43			1.04
30			0.64	60			1.02	47			0.87
								48			0.73
				Mean	28.84	33.05		49			0.90
				SD	13.74	14.22		51			0.84
				%CV	48	43		52			1.04
				n =	60			53			0.88
								54			0.79
								55			0.88
								56			0.99
								57			0.66
								60			1.02
								Mean	29.02	32.95	
								SD	11.48	11.88	
								%CV	40	36	
								n =	40		

The individual subject AUEC(0-24) data represent average value of left and right arm replicates.

Shaded cells at the left indicate test and reference product values used for bioequivalence comparisons, as these subjects showed D2/D1 >1.25

Fig. 1: Correlation between AUEC(0-24) vales based on chromameter and visual assessment of vasoconstriction



BIOAVAILABILITY Disk to Dup To Bio

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

NEW CORRESP

8/20/96

RECEIVED

AUG 2 2 1996

GENERIC DRUGS

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

RE: Hydrocortisone Valerate Topical Cream, 0.2%
ANDA#74-489
Bioequivalence Deficiency Response

Dear Mr. Sporn:
Reference is made to our ANDA for Hydrocortisone Valerate Topical Cream, 0.2% and to the Agency's letter of 5/13/96.

Accompanying this letter are our responses to the Agency's questions. Also included is a data diskette to facilitate review. A print out of the disk's content is provided in the last section of this submission.

Sincerely,

W.E. Brochu, Ph.D.
Director, Regulatory Affairs

ANDA 74-489

MAY 13 1996

Copley Pharmaceutical Inc.
Attention: W. E. Brochu
Canton Commerce Center
25 John Road
Canton, MA 02021

Dear Dr. Brochu:

Reference is made to the Abbreviated New Drug Application, and the amendments submitted on December 15, 1995 and April 1, 1996, for Hydrocortisone Valerate Topical Cream, 0.2%.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. The method of drug application and removal used in the pivotal bioequivalence study submitted on December 15, 1995 was "Staggered application and Synchronized removal". On the other hand, the pilot study submitted on March 1, 1995 used Synchronized application and Staggered removal. The methods for drug application and removal were not consistent between the two studies. Since it is not certain if the ED_{50} value for a given reference listed formulation remains the same using either method of drug application and removal, the June 2, 1995, OGD guidance (pp 17) recommended that the method of drug application and removal should be consistent between pilot and pivotal studies.

   The use of different methods of drug application and removal for the pilot and pivotal studies requires justification. Provide evidence that, using of the "Staggered application and Synchronized removal" method, the ED_{50} for the reference listed drug, Westcort® 0.2% cream continues to be approximately 1.5 hours. The supporting data should be submitted as an amendment to this ANDA.

2. Calculation of AUEC for visual assessment of skin blanching was based on raw visual scores, even though untreated sites for several subjects were scored >0. Recalculate the AUEC data based on visual scoring using the same data corrections as used for the chromameter readings. The correct AUEC values should be used for calculation of 90% confidence intervals. Please submit the revised data in an electronic file.

3. Provide data (mean and %CV) in a tabular format indicating intra- and inter-site precision of the assay. A summary of intra- and inter-operator precision should also be provided.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment must address all of the comments presented in this letter. Should you have questions, please call Mark Anderson, Project Manager, at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APR 16 1996

Hydrocortisone Valerate
Topical Cream, 0.2%
ANDA #74489
Reviewer: Gur J.P. Singh.
File #74489S.D95

Copley
25 John Road
Canton, Mass 02021
Submission Dates:
December 15, 1995,
April 1, 1996.

Review of a pharmacodynamic bioequivalence study

The sponsor has submitted a pharmacodynamic bioequivalence study based on comparison of vasoconstrictor effects of its hydrocortisone valerate 0.2% cream to the reference product, Westcort[R] 0.2% cream manufactured by Westwood Squibb. Dose durations used for this study were the same as recommended, in the Division of Bioequivalence letter of June 27, 1995, upon acceptance of the pilot study submitted by the sponsor on Mach 1, 1995. In the June 27 letter, the sponsor was advised that the pivotal bioequivalence study should be conducted according the Office of Generic Drugs (OGD) guidance.

The methodology employed by the sponsor to determine the bioequivalence of its hydrocortisone valerate formulation is based on the pilot-pivotal study design recommended the OGD guidance. The methods of subject selection, treatment randomization, data collection and statistical analysis are consistent with those recommended in the OGD guidance. However, the review of the bioequivalence study has revealed the deficiencies described below. Therefore, a complete review of this application will be differed till the sponsor has provided a satisfactory response to the following deficiency:

DEFICIENCIES

1. The method of drug application and removal used in the pivotal bioequivalence study submitted on December 15, 1995 was "Staggered application and Synchronized removal". On the other hand, the pilot study submitted on March 1, 1995 used Synchronized application and Staggered removal. Therefore, the methods for drug application and removal were not consistent between the two studies. Since it is not certain if the ED_{50} value for a given reference listed formulation remains the same using either method of drug application and removal, the June 2, 1995, OGD guidance (pp 17) recommended that the method of drug application and removal should be consistent between pilot and pivotal studies.

   The firm should justify the use of different methods of drug application and removal for pilot and pivotal studies. It should provide evidence that, using the "Staggered application and Synchronized removal" method, the ED_{50} for the reference listed drug, Westcort[R] 0.2% cream remains to be approximately 1.5 hours. The supporting data should be submitted as an amendment to this ANDA.

2. Calculation of AUEC for visual assessment of skin blanching was based on raw visual scores, even though untreated sites for several subjects were scored >0. The sponsor should recalculate the AUEC data based on visual scoring using the same data corrections as used for the chromameter readings. The correct AUEC values should be used for calculation of 90% confidence intervals. The sponsor is requested to submit the revised data in an electronic file.

3. The sponsor should provide data (mean and %CV) in tabulated form indicating intra- and inter-site precision of the assay. A summary of intra- and inter-operator precision should also be provided.

RECOMMENDATION

1. The *in vivo* bioequivalence study submitted by Copley Pharmaceuticals comparing its hydrocortisone valerate 0.2% cream to the reference product, Westcort[R] 0.2% cream manufactured by Westwood Squibb, has been found to be incomplete by the Division of Bioequivalence due to deficiency #1-2.

The sponsor should be informed of deficiency #1-3.

Gur J.P. Singh, Ph.D.
Review Branch II
Division of Bioequivalence.

RD INITIALED RPatnaik
FT INITIALED RPatnaik: /S/ 4/16/96

CONCUR: /S/ DATE 4/16/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence.

c
6

Disk to Dup

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

4/1/96

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

RE: Hydrocortisone Valerate Cream 0.2%
ANDA# 74-489
Bioequivalence Telephone Amendment

Dear Mr. Sporn:

Included with this letter is a computer diskette containing bioequivalence data to facilitate the review of our application. Apparently we inadvertently omitted including the diskette.

Sincerely,

W.E. Brochu, Ph.D.
Director, Regulatory Affairs

Copley Pharmaceutical Inc.
25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

12/20/95 Fax Copy

Charles Ganley, M.D. 12/15/95
Acting Director,
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II Room 150
7500 Standish Place
Rockville MD 20855-2773

Re: Hydrocortisone Valerate Cream USP, 0.2%
ANDA# 74-489
Pivotal Bioequivalence Study Report

Reference is made to our ANDA submitted on 3/28/94, our submission of pilot bioequivalence data (study # 9412301) on 10/4/94 and its amendment of 1/23/95. Reference is also made to the Agency's letters of 5/19/94 and 6/27/95.

has recently completed study #9412304 in Copley's behalf. The protocol for this study follows the Agency's guidelines and incorporates refinements discussed by the Agency and This study provides pivotal bioequivalence data which demonstrates bioequivalence of Copley's product to the reference product, Westcort. Two (2) copies of this study report are being submitted, an archival copy and a pharmacokinetic reviewer's copy. The latter copy includes a 3.5 inch diskette of the data contained in the report for the reviewer's convenience.

While have conducted this trial on Copley's behalf, we request that any questions related to this submission or any other aspect of this application be directed to me at Copley Pharmaceutical, Inc.

With this submission we believe our application to be complete and consistent with all Agency requirements. We respectfully request the Agency's review of this application.

Sincerely,

W.E. Brochu, Ph.D.
Director, Regulatory Affairs
617-575-7520

ORIGINAL

Copley Pharmaceutical Inc.
25 John Road
Canton Commerce Center
Canton, Massachusetts 02021
(617) 821-6111
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Canton (617) 821-4068
Boston (617) 268-4394
N.J. (201) 894-1553

ANDA# 74-489
Hydrocortisone Valerate Cream 0.2%
Protocol Review

January 23, 1995

Roger Williams, M.D.
Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855-2773

ORIG NEW CORRES

Dear Dr. Williams:

Enclosed is an amendment to the study report (Study# 9412301) and the proposed protocol which were submitted on October 3, 1994, for your review.

As a result of discussion between Dr. Singh of the Division of Bioequivalence and Mr. Charles Bon of raw data submitted for study 9412301 was fit into the Emax modeling. The Emax model fitting as well as a revised protocol are enclosed in this amendment for your review.

Thank you very much for your consideration.

Sincerely yours,

Whe-Yong Lo
Regulatory Affairs

RECEIVED
JAN 25 1995
GENERIC DRUGS

Two copies enclosed.

T-Con

3/28/96: J. Gross

RE: ANDA 74-489
P 94-089
Hydrocortisone Val 0.2%

FILE

Action:

Dr. Brochu was contacted and advised that the 10/3/94 protocol was not acceptable in light that a new guidance on Topical corticosteroids has been issued dated 6/2/95. Bill Brochu advised me that a study had already been submitted using the new guidance.

Internal Action:

1. This t-Con will serve to close this document.

Attachment-1

Date of Review: November 3, 1995

Consultative Review of BIO 94-089
(Referred by Division of Bioequivalence, HFD-650)

Sponsor: Copley Pharmaceutical, Inc.
Canton, MA 02021

Product: Hydrocortisone Valerate Cream, 0.2%

Purpose of Submission: To request guidance concerning a proposed bioequivalence study (vasoconstrictor assay) comparing the Copley product to Westcort Cream, 0.2%.

Date of Submission: October 3, 1994

Background: The vasoconstrictor assay has been used for some time as the test by which the relative potency of topical corticosteroid formulations is established. Because vasoconstrictor methodology was not standardized, and because questions have been raised about the ability of this methodology to detect differences in the potency of topical steroid products, the office of Generic Drugs (with consultation from this Division) has devised new methods to test the bioequivalency of topical steroids. An Interim Guidance for the performance of bioequivalence studies of topical steroids was issued on July 1, 1992. This protocol is based on that Guidance. The Guidance was altered in late 1994.

Investigator:

Protocol Review:

A. Study design: This will be a single blind, randomized application study to compare the potential of Copley's hydrocortisone valerate 0.2% cream and Westcort Cream 0.2% to cause vasoconstriction.

B. Patient Inclusions: The following is taken directly from the sponsor's submission:

1. Asymptomatic women non-tobacco-using, 18 to 50 years of age, inclusive.

2. Weight within $\pm$ 15 % of the ideal weight for height and body frame as described in the "Table of Desirable Weights of Adults", Metropolitan Life Insurance Company, 1983.

3. Good health as determined by evaluation of a medical history and vital sign assessment prior to study initiation.

4. A negative pregnancy test at screening and prior to dosing.

5. Signed informed consent form which meets all criteria of current FDA regulations.

C. Patient Exclusions: The following is taken directly from the sponsors submission:

1. History of allergy to hydrocortisone, to any corticosteroid, or to any creams, lotions, ointments, or cosmetics.

2. Significant history or current evidence of chronic infectious disease, heart disease, pulmonary obstructive disease, hepatic or renal disease, bronchial asthma, or hypertension.

3. Any skin condition or coloration which would interfere with assessment of skin blanching.

4. Use of any systemic or topical corticosteroid within 30 days of dosing.

5. Medical condition requiring regular treatment with prescription drugs.

6. History of any drug hypersensivity or intolerance which, in the opinion of the Investigator, would compromise the safety of the subject or the study.

7. Use of pharmacologic agents which may affect vasoconstrictor response within 28 days prior to dosing.

8. Use of prescription medications (other than contraceptives) within 7 days of dosing.

9 . Use of any over-the-counter medications within 72 hours of dosing.

10. Ingestion of alcohol or caffeine within 48 hours of dosing.

11. Positive test results for drugs of abuse performed at screening and check-in.

12. Drug or alcohol addiction requiring treatment in the past 12 months.

13. Using any tobacco products in the 90 days prior to screening and throughout the study.

D. Method: The following is an outline of the protocol to be performed by the test facility: Six 1.6 cm diameter circular application sites will be designated on the flexor surface of each forearm. The Copley product will be assigned to two of these sites, Westcort Cream 0.2% will be assigned to thr ee of them, and one will be on untreated control.

A 10 microliter application of the active formulations will be applied to the test sites. After two hours, the test cream and two of the reference sites on each arm will be removed. The product at the third reference site will be removed after one hour from one arm and after four hours from the other arm.

The evaluations will be blinded as to the identify of the treatments. The sites will be assessed by chromameter and visually at 4, 6, 9, 12, 15, 18, 24, 27, 30, 36, 42 and 48 hours after dosing. The visual scale for evaluation of skin blanching will be as follows:

0= No pallor; no change from surrounding area.
1= Mild pallor; slight or indistinct outline of application site.
2= Moderate pallor; discernable outline of application site.
3= Intense pallor; distinct outline of application site.

Conclusion/Recommendations:

This protocol differs in some key respects from the revised Guidance for bioequivalence of topical corticosteriods issued in December, 1994 (especially in duration of dosing). Presuming that the proposed vasoconstrictor study has not yet been performed, the sponsor should be referred to the revised Guidance.

/S/

David Bostwick

/S/

Jonathan Wilkin, M.D.

BIOAVAILABILITY

Copley Pharmaceutical Inc.
25 John Road
Canton Commerce Center
Canton, Massachusetts 02021
(617) 821-6111
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Boston (617) 268-4394
N.J. (201) 894-1553

AC

NDA [illegible]

ANDA 74-439
Hydrocortisone Valerate Cream USP, 0.2%

October 3, 1994

Roger L. Williams, M.D.
Director
Office of Generic Drugs (HFD-600)
CDER, FDA
Metro Park North II
7500 Standish Place
Room 150 Rockville, MD 20855-2773

Dear Dr. Williams:

Copley Pharmaceutical Inc., respectively submits for your devision's review a bioequivalence study protocol for Hydrocortisone Valerate Cream, USP, 0.2%. Our Abbreviated New Drug Application (ANDA) was originally submitted on March 28, 1994 and a deficiency letter refusing to file the ANDA was issued on May 19, 1994. The reason for the refusal of filing was the lack of conformance to the July 1, 1992 Guidance for Topical Corticosteroids: In Vivo Bioequivalence and In Vitro Release Methods.

The study protocol (No. 9412303) was designed based on the results of a pilot study, No 941231C which is also included in this amendment for your review.

Thank you for the consideration of our application.

Sincerely yours,

Whe-Yong Lo
Regulatory Affairs

RECEIVED

OCT [illegible]

ANDA 74-489

MAY 19 1994

Copley Pharmaceutical, Inc.
Attention: Bernie Grubstein
25 John Road
Canton Commerce Center
Canton, MA 02021

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated March 28, 1994, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Hydrocortisone Valerate Cream USP, 0.2%

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

> The Office of Generic Drugs Interim Guidance dated July 1, 1992, for Topical Corticosteroids: In Vivo Bioequivalence and In Vitro Release Methods states that any investigations initiated after July 1, 1992, should generally conform to the recommendations of the Interim Guidance. The vasoconstrictor assay you submitted with your application which was initiated April 20, 1993, does not conform to this guidance. Therefore, the bioequivalence information submitted with your application is incomplete.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Khyati Roberts
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

/S/

Robert W. Pollock
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA#74-489
cc:

Endorsement:

F Phillips 5/18/9,

Copley Pharmaceutical Inc.
25 John Road
Canton Commerce Center
Canton, Massachusetts 02021
(617) 821-6111
Fax:
Canton (617) 821-4068
Boston (617) 268-4394
N.J. (201) 894-1553

28 MARCH 1994

Roger L. Williams, M.D.
Director
Office of Generic Drugs (HFD-600)
CDER, FDA
Metro Park North II
7500 Standish Place
Room 150
Rockville, MD 20855-2773

Dear Dr. Williams:

Copley Pharmaceutical Inc., respectfully submits for your division's review our Abbreviated New Drug Application (ANDA) for Hydrocortisone Valerate Cream, USP, 0.2%. This application is in accordance with the guidelines set forth in Section 505(j) of the Federal, Food, Drug and Cosmetic Act.

In support of this application, a bioequivalency study was conducted at

The results of this study effectively demonstrates equivalency in accordance with the Division of Bioequivalence's guidelines of the Copley formulation to that of the branded product, Westcort Cream, 0.2%.

A copy of this application is being sent under separate cover, to the Boston District Office in compliance with the Federal Register Notice of 8 September 1993.

Thank you for the consideration of our application.

Sincerely yours,

Bernie Grubstein
Regulatory Affairs